

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Yat Sun Or

Application No.: 10/763,377 Group Art Unit: 1623

Filed: January 23, 2004 Examiner: Ganapathy Krishnan

Confirmation No.: 7571

For: Bridged Macrocyclic Compounds and Processes for the Preparation Thereof

**APPEAL BRIEF**

Mail Stop Appeal Brief Patents  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

This Replacement Brief is being filed pursuant to 37 CFR 41.37 and the Notification of Non-Compliant Brief dated May 22, 2009. The sections required under 37 CFR 41.37 are set forth below under separate headings.

(1) The Real Party of Interest

The real party of interest in this appeal is Enanta Pharmaceuticals, Inc., by virtue of the Assignment recorded on April 14, 2004 at Reel 014517 and Frame 0053.

(2) Related Appeals and Interferences

This application was the subject of Appeal No. 2008-3651. The Board rendered a Decision on Appeal dated August 25, 2008. A copy of the decision is provided herewith in the Related Proceedings Appendix. To the knowledge of the appellant, the assignee or its representatives, there are no other related appeals or interferences which will directly affect or be directly affected by or have a bearing in the Board's decision in the pending appeal.

(3) Status of the Claims

Claims 1-12 and 16 are pending and rejected. Claims 1-12 and 16 are appealed.

Claims 13-15 have been cancelled.

(4) Status of the Amendments

An Amendment was filed together with a Request for Continued Examination on October 22, 2008. The amendment was entered. In the Office Action mailed November 20, 2008, claims 1-12 and 16 were rejected.

(5) Summary of Claimed Subject Matter

Claim 1 is appealed and is directed to a process comprising the step of reacting a macrocyclic compound characterized by at least two nucleophilic moieties with a bifunctional bridging component characterized by its ability to form  $\pi$ -allyl metal complex in the presence of catalyst, whereby each of two nucleophilic moieties of the macrocyclic compound reacts with said bifunctional bridging component, thereby achieving a bridged macrocyclic product.

Support for claim 1 is found in the specification at page 2, lines 10 to 13, page 8, line 15 to page 9, line 3 and page 22, lines 22-26.

Claim 16 is also appealed and is drawn to the process of Claim 1 wherein each of the two nucleophilic moieties is alkylated by a functional group of the bridging component.

Support for claim 16 is found in the specification at page 8, line 15, to page 9, line 3.

(6) Ground of Rejection to be Reviewed on Appeal

Whether claims 1-12 and 16 are unpatentable under 35 USC 103(a) as being obvious over WO 99/21864 (“Or *et al.*.”).

(7) Argument

Rejection under 35 USC 103(a)

The Examiner has rejected claims 1-12 and 16 under 35 USC 103(a) as being obvious over Or *et al.* The Examiner stated that Or *et al.* teaches a process for making a bridged macrocyclic compound with the bridging components  $H_2N-(CH_2)_m-A-B-D-X$  and  $(CH_2)_2-C=CH_2$ . The Examiner also stated that the macrocyclic compounds disclosed by Or *et al.* have at least two nucleophilic groups and are structurally similar to the macrocyclic compounds used in the claimed process. The Examiner further stated that the second bridging component with the double bond forms a pi-allyl complex with a metal. The Examiner noted that Or *et al.* teaches the use of two separate bridging components, but stated that it would have been obvious to modify the process of Or *et al.* by using a single bifunctional bridging component. According to the Examiner, one of ordinary skill in the art would have been motivated to modify the method of Or *et al.* by using a single bifunctional bridging component because such a modified process requires fewer steps than the process of Or *et al.*

Claims 1-12

Appellant’s method as recited in claim 1 requires use of a single bridging component, while in the method taught by Or *et al.*, two bridging components are separately attached to the macrocycle and then are joined together. Minimizing the number of process steps, which the Examiner cites as the motivation to modify the process of Or *et al.* to obtain the claimed process, is one of several goals in the development of a synthetic process. However, the Examiner appears to argue that the mere recognition that minimizing process steps is desirable *per se* renders obvious any process improvement that may achieve that goal. This is clearly not correct, as motivation must be coupled with a suggestion of the improvement itself. There is, however, no suggestion in Or *et al.* of other

methods for producing bridged macrocycles, and in particular, there is no suggestion of using a single bridging component. Further, the motivation cited by the Examiner existed for the inventors of Or *et al.* to the same extent that it would for any other synthetic chemist. However, despite this generalized motivation, Or *et al.* developed a multistep process that, *inter alia*, requires the use of two bridging components which are then linked. Yat Sun Or, Ph.D., the first named inventor of the Or *et al.* reference and the inventor of the instant application, is a named inventor on 67 issued US patents in the field of macrolide chemistry and clearly has significantly greater than ordinary skill in the art. Thus, the Examiner's contention that it would have been obvious to one of ordinary skill in the art, motivated to minimize process steps, to modify the process of Or *et al.* by selecting this group of steps and somehow arrive at the claimed process without even a secondary teaching suggesting a solution to the generalized motivation is clearly incorrect.

The method disclosed by Or *et al.* also teaches away from the use of a single bridging component that reacts with two functional groups of the macrocyclic compound. All of the bridging reactions disclosed by Or *et al.* involve two bridging components which are coupled to the macrocycle before they are joined to complete the bridge. The two macrocycle functional groups employed by Or *et al.* in forming the bridge are never simultaneously present in any intermediate compound. That is, a first macrocyclic compound functional group is reacted with a first bridge component *before the second required macrocycle functional group is even formed*. This is shown in Or *et al.* in Schemes 1, 2 and 3, at pages 34-36, and described at page 26, line 27, to page 33, line 4. In Scheme 1, compound 3 includes a 6-hydroxy group, which is reacted with an alkylating agent to form compound 4, which includes a 6-OR group. Two more transformations are then conducted on the macrocyclic compound to form Compound 6. The structure of Compound 6 in Scheme 2 makes it clear that the 6-OR group represents the first bridge component. In Scheme 2, Compound 6 undergoes a series of transformations to convert the 12-OH group to a 12-(imidazole carboxylic ester) group, forming Compound 10a or 10b. It is this 12-(imidazole carboxylic ester) group of Compound 10a or 10b that reacts with the second bridging component,  $H_2N-(CH_2)_m-A-X^2$ . One skilled in the art would not have been motivated to modify the method of Or *et al.* by using a single bridging component capable of reacting with two functional groups of the macrocyclic compound,

because in the method of Or *et al.* there is never a single intermediate macrocyclic compound that includes both functional groups required for bridge formation.

The method of Or *et al.* differs from Appellant's claimed method in other significant aspects. For example, in the process of Or *et al.*, one of the macrocycle functional groups that reacts with a bridging component is not nucleophilic. As discussed above, the 12- imidazole carboxylic ester moiety produced by Or *et al.* reacts with the nucleophilic primary amine of bridging component  $\text{H}_2\text{N}-(\text{CH}_2)_{m-1}-\text{A}-\text{B}-\text{D}-\text{X}^1$  to form a carbamate (see Or, scheme 3 and page 22, lines 1 to 14). The imidazole carboxylic ester moiety is therefore *electrophilic*, a conclusion supported by Boufi *et al.*, *Langmuir* 2008, 24, 7309-7315 (filed with the Amendment and Response of October 22, 2008 and attached in the Evidence Appendix). Scheme 2 at page 7311 of Boufi *et al.* illustrates the reaction of a cellulosic hydroxyl group with carbonyl diimidazole to form an intermediate imidazole carboxylic ester moiety, which then reacts with a primary amine to form a carbamate. At page 7312, first column, Boufi *et al.* state that carbonyl diimidazole is a reagent that "increases the electrophilic character of the carbonyl group" (i.e., by forming an imidazole carboxylic ester group). Thus, in contrast to Appellants' claimed method, in which *two* nucleophilic groups react with the bridging component, in the process of Or *et al.*, *one* nucleophilic group on the macrocyclic compound reacts with one bridging component, while *one electrophilic* group on the macrocyclic compound reacts with the other bridging component. Thus, Or *et al.* fail to teach the fundamental chemical processes recited in Appellant's claims. Further, the effort expended by Or *et al.* to convert the nucleophilic C-12 hydroxyl group to an electrophilic imidazole carboxylic ester group, clearly teaches away from a process in which a nucleophilic group at C12 reacts with a bridging component.

Or *et al.* does not render the process according to amended claim 1 obvious. The process of Or *et al.* differs from Appellant's claimed process in regard to the number of bridging components employed, the chemistry used to join the bridging components to the macrocycle and the number of synthetic steps required. There is no teaching or suggestion in Or *et al.* of any one of the modifications required to obtain Appellant's process, much less all of the required modifications. The Examiner has clearly failed to establish a prima

facie case of obviousness with respect to Or *et al.* Claims 1-12 are therefore not obvious over this reference, and the rejection of these claims should be reversed.

Claim 16

Claim 16 depends from claim 1 and is, therefore, neither taught nor suggested by Or *et al.* for all of the reasons set forth above for claim 1. In addition, claim 16 specifies that each of the two nucleophilic groups of the macrocycle is alkylated by the bridging component. In contrast, in the method of Or *et al.* as set forth in Schemes 1-3 at pages 34 to 36, only one of the two bridging components is joined to the macrocyclic ring via an alkylation reaction. As shown in Scheme 1 at page 34 (conversion of compound 3 to compound 4) and described at page 27, line 20, to page 28, line 2, the reaction of the C6 hydroxyl group with the bridging component is an alkylation reaction. However, the reaction of the imidazole carboxylic ester group at C12 with the primary amine-containing bridging component is not an alkylation reaction. There is no teaching or suggestion in Or *et al.* of altering the chemistry at C12 to include an alkylation reaction. Thus, the Examiner has failed to establish a prima facie case of obviousness with respect to Or *et al.* Claim 16 is therefore not obvious over this reference, and the rejection of this claim should be reversed.

(8) Claims Appendix

See Attached

(9) Evidence Appendix

See Attached

(10) Related Proceedings Appendix

See Attached

The Conclusion

As the Examiner has failed to establish a prima facie case of obviousness, Appellants request reversal of the rejection and allowance of the application.

Respectfully submitted,

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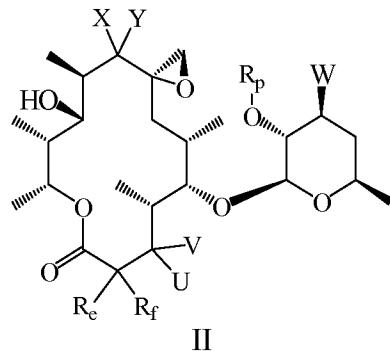
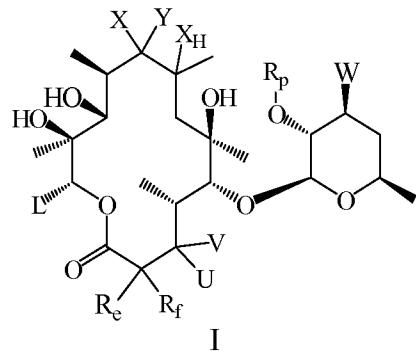
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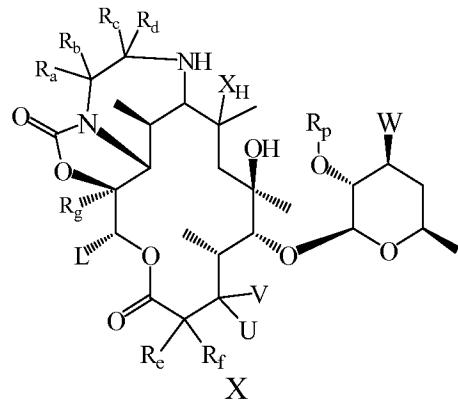
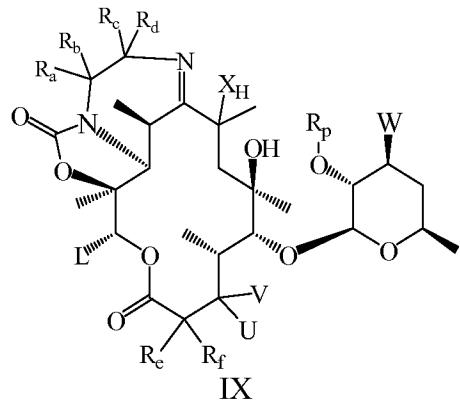
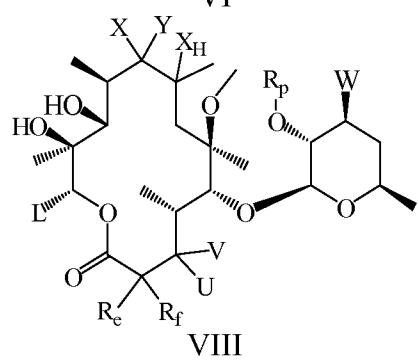
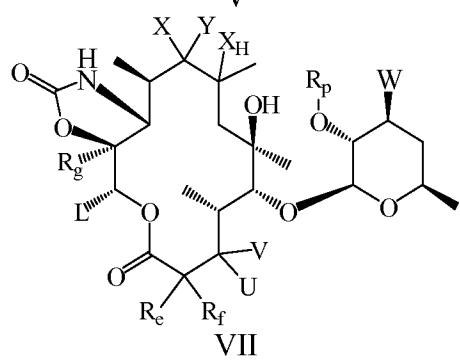
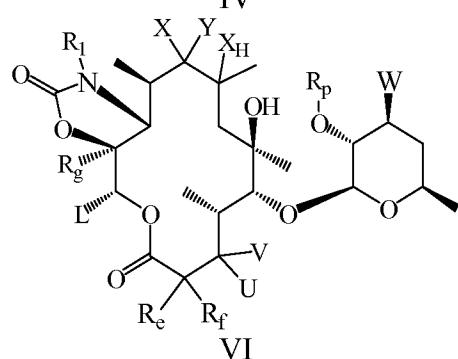
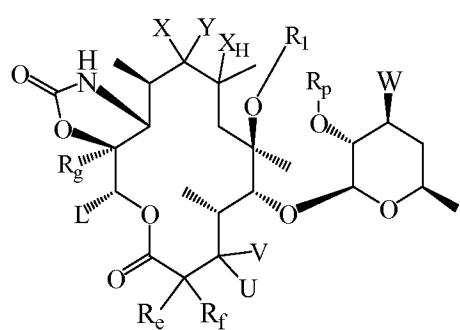
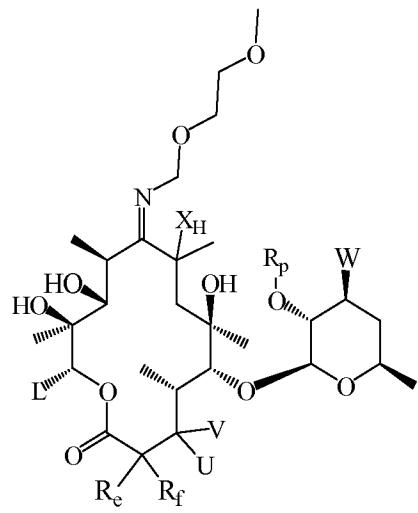
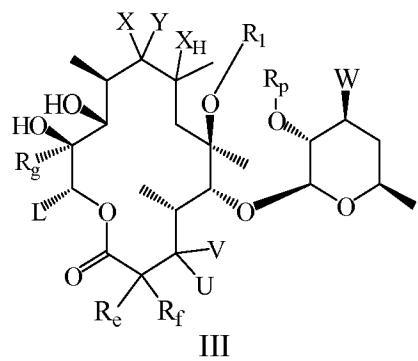
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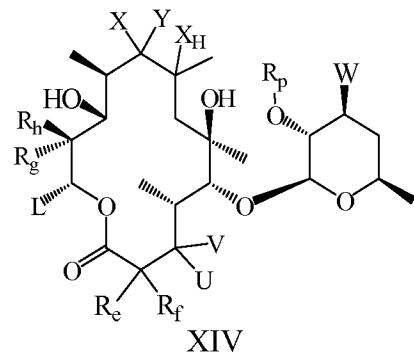
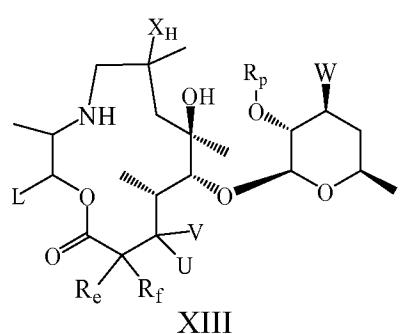
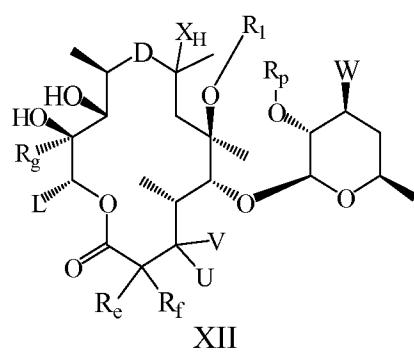
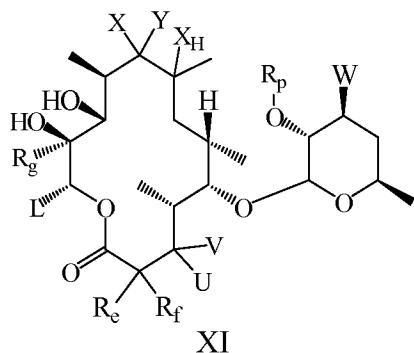
Dated: **June 22, 2009**

**8. Claims Appendix**

1. (Previously Presented) A process comprising the step of reacting a macrocyclic compound characterized by at least two nucleophilic moieties with a bifunctional bridging component characterized by its ability to form  $\pi$ -allyl metal complex in the presence of catalyst, whereby each of two nucleophilic moieties of the macrocyclic compound reacts with said bifunctional bridging component, thereby achieving a bridged macrocyclic product.
2. (Original) The process of claim 1, wherein the macrocyclic compound is a macrolide antibiotic.
3. (Original) The process of claim 1, wherein the macrocyclic compound is an erythromycin derivative.
4. (Original) The process of claim 3, wherein the erythromycin derivative is azithromycin, desmethyl azithromycin, roxithromycin, clarithromycin, telithromycin, or cethromycin.
5. (Original) The process of claim 1, wherein the macrocyclic compound is selected from:







wherein

D is selected from  $-\text{NHCH}_2-$ ,  $-\text{NHCHR}_1-$ ,  $-\text{NHCR}_3\text{R}_4-$ ,  $-\text{NR}_1\text{CH}_2-$ ,  $-\text{NHC(O)-}$ ,  $-\text{NR}_1\text{C(O)-}$ ,  $-\text{NHC(S)-}$ , or  $-\text{NR}_1\text{C(S)-}$ ;

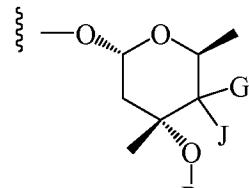
Each  $\text{R}_1$  is independently selected from hydrogen, deuterium, a substituted or unsubstituted, saturated or unsaturated aliphatic group, a substituted or unsubstituted, saturated or unsaturated alicyclic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, saturated or unsaturated heterocyclic group;

$\text{R}_3$  and  $\text{R}_4$  is independently selected from the group consisting of hydrogen, acyl, a substituted or unsubstituted, saturated or unsaturated aliphatic group, a substituted or unsubstituted, saturated or unsaturated alicyclic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, saturated or unsaturated heterocyclic group; or can be taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted heterocyclic or heteroaromatic ring;

L is selected from hydrogen, a substituted or unsubstituted, saturated or unsaturated aliphatic group, a substituted or unsubstituted, saturated or unsaturated alicyclic group, a

substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, or a substituted or unsubstituted heterocyclic group;

one of U or V is hydrogen and the other is independently selected from the group



consisting of: R<sub>1</sub>, OR<sub>1</sub>, OC(O)R<sub>1</sub>, OC(O)NR<sub>3</sub>R<sub>4</sub>, S(O)<sub>n</sub>R<sub>1</sub>, or other carbohydrate or sugar moiety;

or U and V, taken together with the carbon atom to which they are attached, are C=O;

or UV and R<sub>e</sub>R<sub>f</sub>, taken together with the carbon atoms to which they are attached, are -C(R<sub>1</sub>)=CH-;

one of J or G is hydrogen and the other is selected from: R<sub>1</sub>, OR<sub>1</sub>, or NR<sub>3</sub>R<sub>4</sub>;

or J and G, taken together with the carbon atom to which they are attached, are selected from: C=O, C=NR<sub>1</sub>, C=NOR<sub>1</sub>, C=NO(CH<sub>2</sub>)<sub>m</sub>R<sub>1</sub>, C=NNHR<sub>1</sub>, C=NNHCOR<sub>1</sub>, C=NNHCONR<sub>3</sub>R<sub>4</sub>, C=NNHS(O)<sub>n</sub>R<sub>1</sub>, or C=N-N=CHR<sub>1</sub>;

R<sub>a</sub>, R<sub>b</sub>, R<sub>c</sub>, and R<sub>d</sub> are independently selected from -R<sub>1</sub>, -OR<sub>1</sub>, -S(O)<sub>n</sub>R<sub>1</sub>, -C(O)OR<sub>1</sub>, -OC(O)R<sub>1</sub>, -OC(O)OR<sub>1</sub>, -C(O)R<sub>1</sub>, -C(O)NH-R<sub>1</sub>, -NHC(O)-R<sub>1</sub>, -N(R<sub>3</sub>)(R<sub>4</sub>), -NHC(O)-OR<sub>1</sub>, -NHC(O)NH-R<sub>1</sub>, or -OC(O)NH-R<sub>1</sub>;

or R<sub>a</sub> and R<sub>b</sub>, R<sub>a</sub> and R<sub>c</sub>, R<sub>a</sub> and R<sub>d</sub>, R<sub>b</sub> and R<sub>c</sub>, R<sub>b</sub> and R<sub>d</sub>, or R<sub>c</sub> and R<sub>d</sub>, taken together with the carbon atom or atoms to which they are attached, are selected from substituted or unsubstituted alicyclic or substituted or unsubstituted heterocyclic;

one of R<sub>e</sub> and R<sub>f</sub> is selected from hydrogen or methyl, and the other is independently selected from halogen, deuterium, or R<sub>1</sub>;

R<sub>h</sub> is hydroxy;

R<sub>g</sub> is selected from hydrogen, a substituted or unsubstituted, saturated or unsaturated aliphatic group, a substituted or unsubstituted, saturated or unsaturated alicyclic group, a substituted or unsubstituted aromatic group, a substituted or unsubstituted heteroaromatic group, or a substituted or unsubstituted heterocyclic group;

or  $R_g$  and  $R_h$ , taken together with the carbon atom to which they are attached, are selected from an epoxide, a carbonyl, a substituted or unsubstituted olefin, a substituted or unsubstituted alicyclic, a substituted or unsubstituted heterocyclic;

$W$  is  $NR_3R_4$ ;

one of  $X$  and  $Y$  is hydrogen, substituted or unsubstituted aliphatic, and the other is independently selected from: hydroxy,  $-SH$ ,  $-NH_2$ , or  $-NR_1H$ ;

or  $X$  and  $Y$ , taken together with the carbon atom to which they are attached, are selected from:  $C=O$ ,  $C=NR_1$ ,  $C=NOR_1$ ,  $C=NO(CH_2)_mR_1$ ,  $C=NNHR_1$ ,  $C=NNHCOR_1$ ,  $C=NNHCONR_3R_4$ ,  $C=NNHS(O)_nR_1$ , or  $C=N-N=CHR_1$ ;

$R_p$  is selected from hydrogen, acyl, silane, or a hydroxy protecting group;

$X_H$  is selected from hydrogen or halogen;

$m$  is an integer; and

$n$  is 0, 1, or 2.

6. (Previously Presented) The process of claim 5, wherein, for the macrocyclic compound,  $L$  is ethyl.
7. (Previously Presented) The process of claim 5, wherein, for the macrocyclic compound, one of  $X$  and  $Y$  is hydrogen and the other is selected from hydroxy or amino.
8. (Previously Presented) The process of claim 5, wherein, for the macrocyclic compound,  $X$  and  $Y$ , taken together with the carbon atom to which they are attached, are selected from the group consisting of:  $C=O$ ,  $C=NH$ ,  $C=N-OH$ , or  $C=N-NH_2$ .
9. (Previously Presented) The process of claim 5, wherein, for the macrocyclic compound,  $R_g$  is methyl.
10. (Previously Presented) The process of claim 5, wherein, for the macrocyclic compound,  $R_e$  is hydrogen and  $R_f$  is selected from methyl, allyl, or propargyl.

11. (Previously Presented) The process of claim 5, wherein, for the macrocyclic compound, one of U and V is hydrogen and the other is selected from -OH or -O-cladinose.
12. (Previously Presented) The process of claim 5, wherein, for the macrocyclic compound, U and V, taken together with the carbon atom to which they are attached, are C=O.
16. (Previously Presented) The process of Claim 1 wherein each of the two nucleophilic moieties is alkylated by a functional group of the bridging component.

**9. Evidence Appendix**

Boufi *et al.*, *Langmuir* 2008, **24**, 7309-7315.

**10. Related Proceedings Appendix**

Decision on Appeal dated August 25, 2008 for Appeal 2008-3651.